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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,730	05/27/2005	George A. Doherty	21127P	4304

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EXAMINER	
CHENG, KAREN	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 11/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/536,730	DOHERTY ET AL.	
	Examiner	Art Unit	
	Karen Cheng	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-40 is/are pending in the application.

4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 26 is/are rejected.

7)☒ Claim(s) See Continuation Sheet is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 5/27/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1-4 (in part),7-14(in part),16,17-18(in part), 24 (in part), 26 (in part), 40 (in part) .

Continuation of Disposition of Claims: Claims objected to are 1-4 (in part),7-14(in part),16,17-18(in part), 24 (in part), 26 (in part), 40 (in part).

DETAILED ACTION

Claims 1-40 are pending in the instant application.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

Lack of Unity Requirement

Claims 1-40 are drawn to more than one inventive concept (as defined by PCT Rule 13), and accordingly, a restriction is required according to the provision set forth in PCT Rule 13.2.

PCT Rule 13.2 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept (requirement of unity of invention). PCT Rule 13.2 further states unity of invention as referred to in PCT Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. Special technical features, as defined in PCT Annex B, Part 1(b), include those technical features which define a contribution over the prior art.

PCT Annex B, Part 1(e) provides combinations of different categories of claims and states:

"The method for determining unity of invention under Rule 13.2 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application:

(i) in addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product, or

(ii) in addition to an independent claim for a given process, an independent claim for an apparatus or means specifically designed for carrying out the said process, or

(iii) in addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product and an independent claim for an apparatus or means specifically designed for carrying out the said process,..."

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. Due to numerous and widely divergent variables in the compound of Formula (I) for example: $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, **X**, etc., a precise listing of inventive groups cannot be made. The following Groups are exemplary:

Group I: Claims 1-40 (in part) drawn to a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, wherein m is 0, p is 1, G is $-C(R^4)_2$, R^2 and R^3 are joined together to form a 4 or 5-membered monocyclic ring, A, R^1, R^4, R^5, Z, X, R^6 and R^7 are as defined; a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound in accordance with claims 1 in an amount that is effective for treating said immunoregulatory abnormality; and a pharmaceutical composition comprised of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

Group II: Claims 1-40 (in part) drawn to a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, m is 1, p is 1, G is $-C(R^4)_2$, R^2 and R^3 are joined together for form a 4 or 5-membered monocyclic ring, A, R^1, R^4, R^5, Z, X,

R^6 and R^7 are as defined; a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound in accordance with claims 1 in an amount that is effective for treating said immunoregulatory abnormality; and a pharmaceutical composition comprised of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

Group III: Claims 1-40 (in part) drawn to a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, wherein m is 0, p is 1, G is -O-, R^2 and R^3 are joined together for form a 4 or 5-membered monocyclic ring, A, R^1, R^4, R^5, Z, X, R^6 and R^7 are as defined; a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound in accordance with claims 1 in an amount that is effective for treating said immunoregulatory abnormality; and a pharmaceutical composition comprised of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

Group IV: Claims 1-40 (in part) drawn to a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, wherein wherein m is 0, p is 1, G is -O-, R^2 is selected from the group consisting of: hydrogen, halo, hydroxyl, C_{1-6}alkyl and C_{1-5}alkoxy, said C_{1-6}alkyl and C_{1-5}alkoxy optionally substituted from one up to the maximum number of substitutable positions with a substituent independently selected from halo and hydroxyl, R^3 is selected from the group consisting of: hydrogen and C_{1-4}alkyl, optionally substituted with from one up to the maximum number of substitutable

positions with a substituent independently selected from the group consisting of: halo and hydroxyl, A, R^1, R^4, R^5, Z, X, R^6 and R^7 are as defined; a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound in accordance with claims 1 in an amount that is effective for treating said immunoregulatory abnormality; and a pharmaceutical composition comprised of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

Group V: Claims 1-40 (in part) drawn to a compound of Formula I or a pharmaceutically acceptable salt or hydrate thereof, wherein m is 0, p is 1, G is -O-, R^2 and R^3 are joined together for form a 6-membered monocyclic ring, A, R^1, R^4, R^5, Z, X, R^6 and R^7 are as defined; a method of treating an immunoregulatory abnormality in a mammalian patient in need of such treatment comprising administering to said patient a compound in accordance with claims 1 in an amount that is effective for treating said immunoregulatory abnormality; and a pharmaceutical composition comprised of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

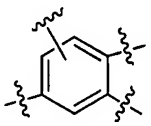
In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted. Again this list is not exhaustive as it would be impossible to write out all groups under the time constraints due to the sheer volume of subject matter instantly claimed. Therefore, applicant may choose to elect a single invention (a product or a process of preparation or a method of use) by identifying another specific embodiment of similar scope not listed in the

exemplary groups of the invention and examiner will endeavor to group the same. The applicant may also choose to elect a single disclosed species or a single disclosed species for a single method of use or preparation and the examiner will endeavor to create a group comprising the elected species

The claims herein lack unity of invention under PCT Rules 13.1 and 13.2 because, pursuant to 37 CFR 1.475(a), **Groups I-V** lack unity of invention since under 37 CFR 1.475:

> Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical feature among those inventions involving one or more of the same or corresponding special technical features. . .those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The structural moiety common to **Groups I-V** is a substituted phenyl group



This technical feature is not a special technical feature because it fails to define a contribution over the prior art (*see* WO Patent 9,809,956). Therefore, Claims 1-40 are not so linked as to form a single general inventive concept, and there is lack of unity of invention. The variables vary extensively and, when taken as a whole, result in vastly different compounds. Additionally, the vastness of the claimed subject matter and the complications in understanding the claimed subject matter impose a serious burden on any examination of the claimed subject matter.

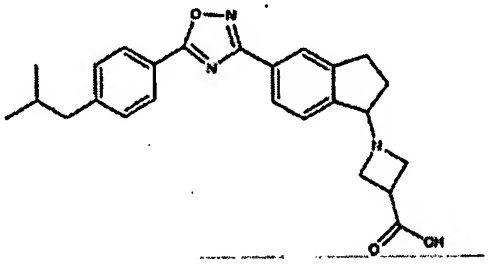
Because the claims do not relate to a single general inventive concept under PCT Rule 13.1 and lack the same or corresponding special technical features, the

claims lack unity of invention and should be limited to a product, a process for the manufacture of said product, ***or*** a method of use.

Applicant is advised that the reply to this requirement, to be complete, must include an election of the invention to be examined even if the restriction requirement is traversed (37 CFR 1.143).

Election

A telephone call was made to Applicant's Representative Raynard Yuro on 10/26/2006 to request an oral election to the above restriction requirement. A provisional election was made *with traverse* to prosecute Group I, which contains the species of the compound depicted in Example 1, p. 20 of the specification,



1-(5-(5-(4-(2-methylpropyl)phenyl)-1,2,4-oxadiazol-3-yl]-2,3-dihydro-1H-inden-1-yl)azetidine-3-carboxylic acid. Affirmation of this election must be made by applicant in replying to this Office action.

Priority

This application is a 371 of PCT/US03/40129 filed on Dec. 16, 2003 and claims the priority of US Serial No. 60/435,381, filed on Dec. 20, 2002. This priority request has been acknowledged for the instant application.

Information Disclosure Statement

The Information Disclosure Statement that was received on May 27, 2005 has been considered fully by the examiner.

Specification

The disclosure is objected to because of the following informalities: Specifically, the amendment filed May 27, 2005 adds continuing data, however, the continuing data is incorrect, specifically, "PCT Application No. PCT/US2003/040129" is incorrect as the application is the PCT Application No. is PCT/US2003/40129

Appropriate correction is required.

Claim Objections

Claims 1 (in part), 2-4 (in part), 7-8 (in part), 10 (in part), 13-14 (in part), 16, 17-18 (in part), 24 (in part), 26 (in part) and 40 (in part) are objected to because of the following informalities: they are dependent on claims, which have been withdrawn from consideration. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*. 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 1 12, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case

The nature of the invention

The nature of the invention is a method of treating an immunoregulatory abnormality by administering to a patient in need a compound of formula I, which has been shown to be $S1P_1$/Edg1 agonists having selectivity over the $S1P_3$/Edg3 receptor.

Page 4 of the specification discloses that the main use for immunosuppressants is in treating bone marrow, organ and transplant rejection, along with the treatment of arthritis, diabetes, multiple sclerosis, psoriasis, etc. Further on p. 26-28, the compounds are specifically disclosed to be immunoregulatory agents useful for treating or preventing autoimmune or chronic inflammatory diseases, including a list of diseases shown on p. 27-28 which include cancer, Alzheimer's, AIDS and etc. and most particularly for treating or preventing bone marrow or organ transplant rejection.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the ad would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of the above listed diseases,

whether or not the disease is affected by the activity of $S1P_1$/Edg1 receptor would make a difference.

Applicants are claiming a method of treating an immunoregulatory abnormality, which can include diseases listed in the specification such as viral infection, including AIDS, cancer, and Alzheimer's by administering a compound of the formula (I). Additionally applicants claim a method of treating or preventing bone marrow or organ transplant rejection. Note this list of diseases is not exhaustive but rather incorporates a selection of the diseases that are encompassed by applicants' method claim.

As such, the specification fails to enable the skilled artisan to use the compound of the formula (I) to treat AIDS. In addition, there is no proof that the claimed compounds have ever been administered to a human or to an animal model. The obstacles to therapeutic approaches and vaccine development with regard to retroviruses associated with AIDS in humans are well documented in the literature. See, for example, Huff {J. Med. Chem. 34(8) 1991, p. 2305-2314} on page 2314. These obstacles include and are not limited to: 1) the extensive genomic diversity associated with HIV, particularly with respect to the gene encoding the envelope protein, 2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a convert form, as well as via free virus transmission, 3) existence of a latent form of the virus, 4) the ability of the retrovirus to traverse the blood brain barrier and 5) the complexity and variation of the elaboration of the disease. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting

therapeutic regimen on its face. In addition, there is no established correlation between in vitro activity and accomplishing treatment of viral infections, especially HIV infections, in vivo, and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the art would not be able to use the compounds of the formula (I) since there is no description of an actual method wherein a viral infection in a host is treated.

Applicants' claims also include the treatment of any cancer. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al. page 531) Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Hortobagyi, p. 974) that the several genes, including p53, bcl-2, c-myc, and c-myb, HER-2/neu, and cyclin D, have all been found in abnormal levels in patients with breast cancer. However, the number and types of mutations necessary for development of breast cancer are not known. These examples illustrate the different cellular

mechanisms believed to be involved in the progression of cancer, and thus showcase the unpredictability in the art, especially in regards to treatment protocols.

It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease. (URL: http://www.ninds.nih.gov/disorders/alzheimersdisease/alzheimersdisease.htm)

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by activation of $S1P_1$/Edg1 receptor, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of $S1P_1$/Edg1 receptor in the progression of these diseases.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is for a list of diseases that the applicants' consider relevant to the activity of an $S1P_1$/Edg1 receptor, listed on p. 26-28. However, applicants do not provide sufficient, or any test results that link the administration of a compound of formula (I) to treatment of any of the aforementioned diseases. A brief assessment of lymphopenia, the decrease of white blood cells, is disclosed on p. 61. However, this test is performed on three mice, which

is not sufficient evidence to support the applicants' claims to the treatment of an immunoregulatory abnormality in a mammalian patient. Results that are found in a mouse do not necessarily translate into other mammals due to the numerous differences in the immune systems of different mammals. Additionally the number of mice tested is insufficient to draw any conclusive statements. There are no working examples present for the treatment of any immunoregulatory abnormalities.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include treatment of diseases that have an immunoregulatory abnormality. Such diseases include AIDS, cancer, Alzheimer's disease, autoimmune and chronic inflammatory diseases (see p. 26-29) and may be associated with the activity of an $S1P_1$/Edg1 receptor.

The quantity or experimentation needed and the level of skill in the art

It would require undue experimentation of one of ordinary skill in the art to ascertain the effectiveness of the compound in treatment of any of the diseases encompassed by the claims. One of skill in the art would first need to determine what diseases could be treated by the modulation of the $S1P_1$/Edg1 receptor and would then need to determine which, if any, of the claimed compounds could actually provide treatment of the disease. Factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. While the level of skills in the pharmaceutical art is high, the quantity of experimentation needed is undue. One of

skill in the art would need to have examples or data supporting the effectiveness of the claimed compound in treating each and every disease claimed due to the unpredictability in the pharmaceutical art. Thus, the specification fails to provide sufficient support of the method of use of the claimed compound in the treatment of immunoregulatory abnormalities or the treatment of all the diseases or conditions listed on p. 26-28 of the specification.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, it is apparent that undue experimentation is necessary because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Therefore, claim 26 is rejected under 35 U.S.C. § 112, 1st paragraph.

Conclusion

A search was made of the prior art, and the closest art was found to be WIPO Pub. No. 03/105771, which discloses compounds with similar core but have a benzene ring alone without a five-membered ring fused to the benzene ring.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cheng whose telephone number is 571-272-6233. The examiner can normally be reached on M-F, 9AM to 5:30PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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